changes at all. A transient erythematous flush of the neck and upper chest was observed in four children, and was the only objective side-effect noted in the series.

Discussion

The murmurs brought out by means of phenylephrine usually became audible about three minutes after the injection, and commonly persisted for 15 to 25 minutes. As stated earlier, the maximum pressor response occurred within two minutes of the injection, and the blood pressure returned to normal within four to eight minutes. Bradycardia occurred as soon as the blood pressure began to rise—that is, about ten seconds after the injection—and lasted three to four minutes. It follows that aortic diastolic murmurs induced by the drug do not depend solely upon the height of the blood pressure and that induced mitral diastolic murmurs do not depend solely upon artificial bradycardia. In fact, aortic diastolic murmurs occasionally developed after the blood pressure and pulse rate returned to normal. It is possible that a damaged aortic valve may leak only after an increased load has been carried for a sufficient time; in other words, that valve strain depends not only upon the size of the load but also upon its duration. Indeed, the fact that the phenylephrine murmur may outlast detectable physiological changes has raised the question whether the drug itself might have caused further valve damage; but all such murmurs have been transient, and this possibility seems improbable.

Mitral diastolic murmurs induced by means of phenylephrine may also bear a similar delayed relationship to the known physiological effects of the drug. As they may still be heard clearly for several minutes after the heart rate has returned to the pre-injection level, their detection cannot be attributed to improved auscultatory perception at slow rates. An augmented mitral blood flow per beat, associated with an increased stroke volume, is more likely to be responsible for the murmur. Functional mitral diastolic murmurs in cases of patent ductus arteriosus and ventricular septal defect have been explained in this way. But the time lag again seems to demand the implication of some other factor.

An obvious possibility is that phenylephrine may increase the stroke volume by a direct stimulating action on the myocardium. At the time of writing only a few physiological studies have been made; these have revealed a rise of jugular venous pressure, right auricular pressure, and pulmonary artery pressure, associated with a slight fall in cardiac output and an increased stroke volume. The duration of these changes and their relationship to bradycardia have not yet been determined in our laboratory.

Summary and Conclusion

Phenylephrine, a sympathomimetic drug with a nor-adrenaline-like action, has been given to 64 patients, of whom 35 had rheumatic carditis.

Transient elevation of the blood pressure and reflex bradycardia occurred in like degree in both non-rheumatic and rheumatic cases with and without carditis.

Transient aortic and mitral diastolic murmurs were induced by means of phenylephrine in many cases of rheumatic carditis, but never in non-rheumatic patients or in cases of rheumatic fever without carditis.

Aortic diastolic murmurs so induced are attributed chiefly to an increased load from transient hypertension straining a damaged aortic valve, mitral diastolic murmurs mainly to

an increased mitral blood flow associated with an augmented stroke volume resulting from reflex bradycardia; but other factors appear to be implicated.

Such murmurs offer clear evidence of valve damage and may be of considerable diagnostic aid.

I am deeply indebted to Dr. Paul Wood for the original suggestion that initiated this work, as well as for all his subsequent encouragement and criticism. I would also like to express my gratitude to Dr. Eric Bywaters for his many helpful suggestions, and to Dr. Gerald Thomas and other colleagues who have assisted at the clinical observations.

EFFECT OF GROWTH HORMONE AND OF CHORIONIC GONADOTROPHIN ON PREPUTIAL GLANDS OF THE FEMALE RAT

BY

H. H. FOURACRE BARNES,* M.B., F.R.C.S.
M.R.C.O.G.

*Assistant, Obstetric Unit, University College Hospital
Gynaecological Surgeon, Hospital for Women, Soho Square
London*

AND

G. I. M. SWYER, D.M., D.Phil., M.R.C.P.

*Consultant Endocrinologist to the Obstetric Department
University College Hospital*

Selye (1951) has recently observed a striking increase in the size of the preputial glands of the female rat treated with growth hormone (somatotrophin, or S.T.H.). He stated: "Preliminary investigations have shown that under suitable experimental conditions, S.T.H. causes marked preputial-gland enlargement within 48 hours. Perhaps the sensitivity of this test might be further augmented by topical application of S.T.H. We mention these preliminary findings only because of the urgent need for a clinically applicable sensitive bio-assay method for the estimation of S.T.H. in biological fluids. Perhaps they will stimulate others to explore such possibilities."

We have been interested for some years in the question of whether an increase in the production of growth hormone by the anterior lobe of the pituitary gland could account for the well-known abnormalities of the foetus in diabetic and prediabetic pregnancies, as well as for the development of frank diabetes in women in the latter state (Barnes and Morgans, 1948; Gilbert, 1949; Barnes *et al.*, 1950). It seemed to us, therefore, that if, following Selye's suggestion, a simple and sensitive method for the assay of growth hormone could be based on the increase in the weight of the preputial glands of the female rat, it might be possible to test directly whether the urinary excretion, for instance, of growth hormone in pregnant diabetics was greater than that of non-diabetic pregnant women in comparable circumstances. As it was certain that chorionic gonadotrophin would be present in high concentration in the body fluids with which we should have to deal, it was important that the effects of this hormone on the preputial glands should also be studied, especially since evidence quoted in Selye's paper suggested that the effect might be far from specific for growth hormone. Mor-

*Lund Research Fellow of the Diabetic Association.

over, as the preputial glands are accessory sex organs, it would be reasonable to suppose that they would be influenced by hormones produced by the gonads and indirectly, therefore, by gonadotrophins.

Preliminary experiments have been carried out to test these possibilities under the simplest conditions, and though the results are disappointing we have thought it worth while to record them.

Experiment 1

Nine young albino female rats, of weights ranging between 47 and 66 g., were used. Three rats served as controls, three received a daily injection of pituitary growth hormone (Armour and Co. J-21609R) equivalent to 1 mg. each, and three received a daily injection of 100 i.u. of chorionic gonadotrophin each. The injections were subcutaneous and were given for three successive days; on the fifth day the rats were killed. Their weights and the weights of the preputial glands, ovaries, and uteri are given in Table I. (Because of the small numbers of animals, means and ranges, not standard deviations, are recorded.)

TABLE I.—Experiment 1: Summary of Effects of Growth Hormone and of Chorionic Gonadotrophin on Weights of Preputial Glands, Ovaries, and Uteri of Rats

Groups	Controls	Growth Hormone	Chorionic Gonadotrophin
Mean body weight (g.)			
Before injections	49.2 (47.1-51.3)	59 (52.9-66)	63.1 (59.5-66)
After ..	62 (56.5-65.5)	74 (65-83.5)	74.8 (75.5-82)
Mean weight of preputial glands			
mg. ..	25 (20-33)	30.8 (27-34.5)	50.6 (47.5-65)
mg./100 g. final body weight ..	40.5 (30.5-52.4)	41.7 (41.3-42.2)	69.3 (60.4-84.5)
Mean weight of ovaries			
mg. ..	21.5 (15-26.5)	22.8 (21.5-25)	57.8 (47-64)
mg./100 g. final body weight ..	37.6 (26.8-44.8)	31 (29.2-33.8)	74.8 (58.5-88.1)
Mean weight of uteri			
mg. ..	71 (33-123)	68 (35-100)	187 (164-208)
mg./100 g. final body weight ..	113.5 (58.4-195)	88.8 (53.9-120)	241 (200-270)

It is clear that, in the dose used, growth hormone has had no detectable effect on the preputial glands, ovaries, or uteri. On the other hand, chorionic gonadotrophin has resulted in definite enlargement of all three organs. We must therefore conclude that the experimental procedures we have followed would be totally unsuitable for estimating the growth hormone content of a body fluid which also contained chorionic gonadotrophin.

Experiment 2

Although our supplies of growth hormone were very limited, it seemed that an attempt should be made to verify the activity of the preparation, in view of the disappointing results described above. Accordingly, we injected each of two female albino rats with 0.5 mg. a day for seven days, and on the eighth day determined the increase in body weight and the weights of the preputial glands and ovaries. There were also two uninjected controls of similar initial body weights. The results, given in Table II, demonstrate clearly the growth-promoting efficacy of the preparation used, the treated animals showing a mean increase in weight, per 100 g. original body weight, 72% greater than that of the controls. On the other hand, the mean excess of the weights of the preputial glands and ovaries, per 100 g. final body weight, of the treated animals as compared with the controls was 22% and 25.5% respectively. It

TABLE II.—Experiment 2: Summary of the Effects of Growth Hormone on the Growth and Weights of Preputial Glands and Ovaries of Rats

Groups	Controls	Growth Hormone (3.5 mg. Over 7 Days)	% Increase in Case of Treated Animals
Initial body weight (g.)	209 212	218 214	
Final ..	220 226.5	241.5 235.5	
Mean increase in body weight per 100 g. original weight (g.)	6.05	10.4	72*
Preputial glands (mg.)	104 103	122 134	
Preputial glands mg./100 g. final body weight—means	46.3	56.5	22
Ovaries (mg.)	70 94	109 110.5	
Ovaries mg./100 g. final body weight—means	36.6	46	25.5

* Note that this is the percentage increase of weight gained by the treated animals, not the percentage excess of final body weight over that of the controls. It is therefore not comparable with the two lower figures in the same column, though these, however, are comparable one with another.

therefore seems that daily injections of growth hormone for three days may produce no appreciable effects, whereas a similar total dose spread over seven days will have clear effects; and that the preputial glands are no more sensitive to growth hormone than the ovaries.

Our results do not seem to bear out Selye's suggestion that the rat's preputial gland is likely to prove a sensitive test object for the bio-assay of growth hormone in biological fluids, but further conclusions are not warranted by the scanty experimental data we have presented.

Summary

Preliminary experiments to inquire whether the preputial glands of the female rat would be a suitable test object for the assay of growth hormone have not borne out Selye's encouraging view. Chorionic gonadotrophin caused a much greater increase in their weight than did growth hormone, which produced at least as much relative increase in the ovarian weight.

We wish to thank Dr. Irby Bunding, of Messrs. Armour and Co., for providing the growth hormone.

REFERENCES

- Barns, H. H. Fouracre, Lindan, O., Morgans, M. E., Reid, E., and Swyer, G. I. M. (1950). *Lancet*, 2, 841.
— and Morgans, M. E. (1948). *J. Obstet. Gynaec. Brit. Emp.*, 55, 449.
Gilbert, J. A. L. (1949). *British Medical Journal*, 1, 702.
Selye, H. (1951). *Ibid.*, 1, 263.

In his report for 1950 the school medical officer of health for Manchester remarks: "It is sad that the lip-reading class remains small. We know there must be quite a large number of children in the city deaf enough to need this kind of training, but fewer than half those recommended by the doctors at the audiometer clinic avail themselves of the opportunity. While most parents eagerly accept medical treatment for their deaf children, letting them learn lip-reading probably seems to many tantamount to admitting that some deafness is likely to be permanent, and this is more than they can bring themselves to do. It is a great pity, for the partially deaf pupil is gravely handicapped in school and needs all the assistance he can get. He is not deaf enough to be sent to the school for the deaf, and yet cannot do himself justice in an ordinary school. Ideally, he should be attending a class for the hard-of-hearing, where he would find special conditions for the academic part of his education while participating in the games and practical activities of his schoolfellows with normal hearing, and avoiding the disadvantages of being cut off from their society. Until we have such a facility in Manchester the speech clinic must do what it can for those whose parents will allow them to be helped."